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Total Airway Count on Computed Tomography and the Risk of Chronic Obstructive Pulmonary Disease Progression. Findings from a Population-based Study

Kirby, Miranda ; Tanabe, Naoya ; Tan, Wan C ; Zhou, Guohai ; Obeidat, Ma'en ; Hague, Cameron J ; Leipsic, Jonathon ; Bourbeau, Jean ; Sin, Don D ; Hogg, James C ; Coxson, Harvey O

Abstract: RATIONALE Studies of excised lungs show that significant airway attrition in the "quiet" zone occurs early in chronic obstructive pulmonary disease (COPD). OBJECTIVES To determine if the total number of airways quantified in vivo using computed tomography (CT) reflects early airway-related disease changes and is associated with lung function decline independent of emphysema in COPD. METHODS Participants in the multicenter, population-based, longitudinal CanCOLD (Canadian Chronic Obstructive Lung Disease) study underwent inspiratory/expiratory CT at visit 1; spirometry was performed at four visits over 6 years. Emphysema was quantified as the CT inspiratory low-attenuation areas below -950 Hounsfield units. CT total airway count (TAC) was measured as well as airway inner diameter and wall area using anatomically equivalent airways. MEASUREMENTS AND MAIN RESULTS Participants included never-smokers (n = 286), smokers with normal spirometry at risk for COPD (n = 298), Global Initiative for Chronic Obstructive Lung Disease (GOLD) I COPD (n = 361), and GOLD II COPD (n = 239). TAC was significantly reduced by 19% in both GOLD I and GOLD II compared with never-smokers ($P < 0.0001$) and by 17% in both GOLD I and GOLD II compared with at-risk participants ($P < 0.0001$) after adjusting for low-attenuation areas below -950 Hounsfield units. Further analysis revealed parent airways with missing daughter branches had reduced inner diameters ($P < 0.0001$) and thinner walls ($P < 0.0001$) compared with those without missing daughter branches. Among all CT measures, TAC had the greatest influence on FEV ($P < 0.0001$), FEV/FVC ($P < 0.0001$), and bronchodilator responsiveness ($P < 0.0001$). TAC was independently associated with lung function decline (FEV, $P = 0.02$; FEV/FVC, $P = 0.01$). CONCLUSIONS TAC may reflect the airway-related disease changes that accumulate in the "quiet" zone in early/mild COPD, indicating that TAC acquired with commercially available software across various CT platforms may be a biomarker to predict accelerated COPD progression.

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ORIGINAL ARTICLE

Total Airway Count on Computed Tomography and the Risk of Chronic Obstructive Pulmonary Disease Progression

Findings from a Population-based Study

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Abstract

Rationale: Studies of excised lungs show that significant airway attrition in the "quiet" zone occurs early in chronic obstructive pulmonary disease (COPD).

Objectives: To determine if the total number of airways quantified *in vivo* using computed tomography (CT) reflects early airway-related disease changes and is associated with lung function decline independent of emphysema in COPD.

Methods: Participants in the multicenter, population-based, longitudinal CanCOLD (Canadian Chronic Obstructive Lung Disease) study underwent inspiratory/expiratory CT at visit 1; spirometry was performed at four visits over 6 years. Emphysema was quantified as the CT inspiratory low-attenuation areas below −950 Hounsfield units. CT total airway count (TAC) was measured as well as airway inner diameter and wall area using anatomically equivalent airways.

Measurements and Main Results: Participants included never-smokers ($n = 286$), smokers with normal spirometry at risk for COPD ($n = 298$), Global Initiative for Chronic Obstructive Lung Disease (GOLD) I COPD ($n = 361$), and GOLD II COPD ($n = 239$). TAC was significantly reduced by 19% in both GOLD I and GOLD II compared with never-smokers ($P < 0.0001$) and by 17% in both GOLD I and GOLD II compared with at-risk participants ($P < 0.0001$) after adjusting for low-attenuation areas below −950 Hounsfield units. Further analysis revealed parent airways with missing daughter branches had reduced inner diameters ($P < 0.0001$) and thinner walls ($P < 0.0001$) compared with those without missing daughter branches. Among all CT measures, TAC had the greatest influence on FEV_1 ($P < 0.0001$), FEV_1/FVC ($P < 0.0001$), and bronchodilator responsiveness ($P < 0.0001$). TAC was independently associated with lung function decline (FEV_1, $P = 0.02$; FEV_1/FVC, $P = 0.01$).

Conclusions: TAC may reflect the airway-related disease changes that accumulate in the "quiet" zone in early/mild COPD, indicating that TAC acquired with commercially available software across various CT platforms may be a biomarker to predict accelerated COPD progression.

Keywords: computed tomography; chronic obstructive pulmonary disease; chronic obstructive pulmonary disease progression; emphysema; small airway disease

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A complete list of members of the CanCOLD Collaborative Research Group may be found before the beginning of the References.

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At a Glance Commentary

Scientific Knowledge on the Subject: There is evidence that massive destruction of terminal bronchioles is well established before the appearance of emphysematous destruction in chronic obstructive pulmonary disease (COPD). However, it is unknown whether this reduction in small airway number is reflected in the more central airways evaluated *in vivo* using computed tomography (CT) in individuals with mild COPD independent of emphysema. To our knowledge, there have been no studies investigating CT airway count and the relationship with lung function decline in participants with early/mild COPD.

What This Study Adds to the Field: In a population-based sample of participants we demonstrate that CT airway count is significantly reduced in mild COPD independent of emphysema, that missing airways are spatially related to parent airway wall thinning and luminal narrowing/tapering, and that reduced CT airway count is significantly and independently associated with rapid decline in lung function over time. These findings indicate that early airway-related changes can be assessed *in vivo* using CT acquired in at-risk individuals at multiple sites and across various CT platforms, highlighting the feasibility and applicability of these findings. Most importantly, these findings also suggest that early intervention may be required for optimal disease modification.

Airflow limitation measured during a forced expiratory maneuver is the physiologic hallmark of chronic obstructive pulmonary disease (COPD) (1). Although the site of this obstruction has been localized to the small conducting airways less than 2 mm in diameter (2), much remains to be learned about the pathology responsible for this obstruction to airflow. To date, the most detailed studies of the structural features of this obstruction to flow have been performed using micro computed tomography (micro-CT) images of samples removed from excised lungs donated by patients with very severe COPD treated by lung transplantation (3). These investigations show there is massive destruction of the terminal bronchioles before emphysematous lesions become visible at the approximate 15-μm spatial resolution provided by micro-CT, and long before they are large enough to be visible at the approximate 1-mm spatial resolution provided by multidetector CT.

Advanced CT image processing now makes it possible to segment the airway tree from the trachea to the smaller airways at the resolution of the CT systems, airways approximately 2 mm in diameter. Therefore, the purpose of this study was to use commercially available software (VIDA Diagnostics, Inc.) to segment the airway tree and count the total number of CT airways in CanCOLD (Canadian Chronic Obstructive Lung Disease) participants. Importantly, CanCOLD is a multicenter, population-based study (4) and therefore participants represent mild, more ambulant presentations of COPD. We hypothesized that the narrowing, obstruction, and/or destruction of the terminal bronchioles that occur before emphysema development (3) is also reflected in the proximal airways and can be quantified using the CT total airway count (TAC). Furthermore, we hypothesized that TAC is significantly reduced in mild COPD compared with never-smokers, and is significantly associated with lung-function decline over time.

Methods

Study Participants

Written informed consent was obtained from participants in the multicenter CanCOLD study, which was approved by the institutional review boards at each study site. Briefly, CanCOLD is a prospective, multicenter (nine sites in six Canadian provinces), longitudinal study investigating individuals greater than 40 years of age that were randomly selected from the general population (4). COPD was defined spirometrically according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria (5). A flowchart detailing how participants were selected for analysis is shown in Figure 1. For the participants evaluated in this study, the mean time between visit 0 and visits 1, 2, and 3 was (mean ± SD) 2.5 ± 1.7 years, 4.4 ± 1.7 years, and 5.9 ± 1.8 years, respectively.

Pulmonary Function Tests

Spirometry was performed for measurement of the FEV_1 and FVC before and 15 minutes following inhalation of 200 μg albuterol according to American Thoracic Society guidelines (6–8). Bronchodilator response (BDR) was defined as the percent change in FEV_1 (L) after bronchodilator inhalation [(FEV_1 post-BD − FEV_1 pre-BD)/FEV_1 pre-BD] × 100. Whole-body plethysmography was performed for measurement of the residual volume/total lung capacity (RV/TLC) ratio and $D_{L_{CO}}$.

CT Image Acquisition

CT images were acquired at each of the nine sites using CT systems of various makes and models with the participant supine at suspended full-inspiration and full-expiration from apex to base of the lung as previously described (4). The CT parameters for image acquisition are as follows: 100 kVp, 50 mAs, 0.5-second gantry rotation, pitch of 1.375, and 1.0- or 1.25-mm slice thickness, contiguous slices. The standard or soft tissue reconstruction kernel was used for quantitative analysis.

CT Image Analysis

CT images were evaluated using the Apollo 2.0 software package (VIDA Diagnostics, Inc.) and the VIDA Diagnostics, Inc., clinical image analysis service, that is ISO13485 certified for quality control. Briefly, to generate the CT airway measurements, the CT airway tree was first automatically segmented and the airways were automatically labeled from the trachea to the subsegmental bronchi. Airway segmentation and labeling were visually verified by a highly trained analyst and edited if required; a second analyst then performed peer review of the segmentation and labeling for quality control. A detailed description of VIDA Diagnostics, Inc., clinical image analysis service airway segmentation workflow is provided in the online supplement. The high reproducibility of airway measurements generated by VIDA Diagnostics, Inc., clinical image analysis services has been previously reported (9).

The TAC measurements were obtained by summing all airway segments from the segmented airway tree. Airway counts were

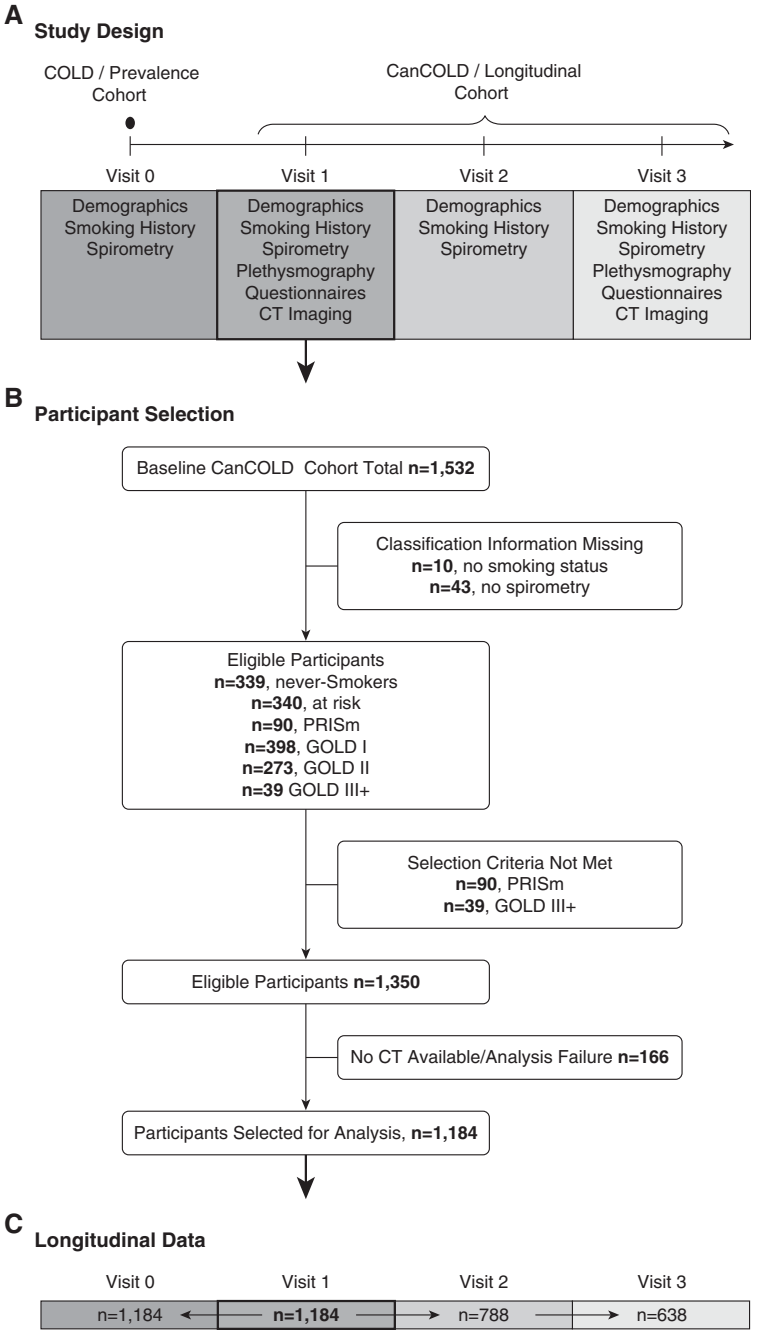

Figure 1. Subject selection flowchart. (*A*) Participants included in the COLD (Chronic Obstructive Lung Disease) prevalence study were selected to participate in the longitudinal CanCOLD (Canadian Chronic Obstructive Lung Disease) study as previously described (4). (*B*) The baseline CanCOLD cohort included $n = 1{,}532$ participants. Participants with no classifying information, namely no information related to smoking status ($n = 10$) and spirometry ($n = 43$), were excluded. For those participants classified, participants with preserved FEV_1/FVC ratio but decreased FEV_1, also known as preserved ratio but impaired spirometry ($n = 90$), were excluded. Given the paucity of GOLD III+ participants ($n = 39$), they were also excluded from our analysis. Finally, participants for whom computed tomography images could not be analyzed for any reason were excluded ($n = 166$). The final number of $n = 1{,}184$ participants were included in the analysis. (*C*) For the participants selected for the analysis, spirometry measurements were obtained from the original COLD study and from the ongoing longitudinal CanCOLD study to evaluate the lung function trajectory. CT = computed tomography; GOLD = Global Initiative for Chronic Obstructive Lung Disease; PRISm = preserved ratio but impaired spirometry.

also generated by airway generation starting at the trachea (generation 0) to generation 10 and by airway diameter. Only anatomically equivalent segmental, subsegmental, and sub-subsegmental airways for five predetermined airway paths (RB1, RB4, RB10, LB1, and LB10) were used to generate airway inner lumen area, lumen diameter, and airway wall area (9). Subsegmental airway inner lumen diameter tapering was defined as the ratio of the airway lumen diameter measurements at points 30% and 70% along the length of the airway segment between the parent branch point (0%) and the daughter branch point (100%). Pi10 was defined as the wall thickness of a theoretical airway with a lumen perimeter of 10 mm (10) and was calculated using anatomically equivalent airways.

Emphysema was quantified on full-inspiration CT images using the low-attenuation areas of the lung below −950 Hounsfield units (HU) (LAA_{950}) (11–13). Gas trapping was also quantified using full-expiration CT images as the low-attenuation area of the lung below −856 HU (LAA_{856}) (14, 15). The presence or absence of bronchiectasis (binary variable) was visually scored by radiologists blinded to participants' clinical characteristics. In a subgroup analysis of 494 participants that were randomly selected for a separate study ($n = 140$ never-smokers, $n = 103$ at-risk, $n = 149$ GOLD I, $n = 102$ GOLD II), CT parametric response mapping (PRM) functional small airway disease (fSAD) and emphysema measurements were generated by registering images acquired at full-inspiration to images acquired at full-expiration and applying established thresholds, as previously described (16).

Statistical Analysis

All statistical analysis was performed using SAS version 9.4 software. A one-way ANOVA with a Tukey test for multiple comparison correction was performed for statistical comparison between never-smokers, at-risk, GOLD I, and GOLD II COPD groups for participant demographic, pulmonary function, and CT measurements. For categorical variables, a Fisher exact test was used. An analysis of covariance was used for statistical comparison of TAC measurements between all groups (never-smoker, at-risk, GOLD I, and GOLD II) adjusted by confounding

variables (age; sex; race; pack-years; smoking status; body mass index [BMI]; history of asthma; history of tuberculosis; history of heart disease, systemic hypertension, or diabetes mellitus; history of bronchiectasis; FEV_1% predicted; CT air volume; and CT scanner model); a separate analysis of covariance was performed that was also adjusted by LAA_{950} in addition to other confounding variables.

For comparison of airway inner diameter, airway wall area, and inner diameter tapering measurements for all subsegmental airways in participants with daughter branches missing or not missing, we used a Mann-Whitney *t* test. We determined if subsegmental parent airways were missing their sub-subsegmental daughter branches using the output file exported by the Apollo 2.0 software; all airway segments were assigned a unique identifier that linked each parent airway to the corresponding daughter branches. We conservatively defined participants with missing daughter branches if parent airways with at least one of their daughter branches was missing. A multivariable logistic regression analysis was also used to determine if parent airway lumen diameter, airway wall area, and inner diameter tapering measurements remained significantly associated with daughter branches missing or not missing (binary variable) after adjusting for potential confounding variables.

In the subset of participants with inspiration-to-expiration PRM measurements, a multivariable linear regression analysis was used to determine the associations for TAC using all CT measurements (PRM-fSAD, PRM-emphysema, Pi10, lumen area) adjusted by confounding variables. A multivariable regression analysis was used to determine variables with significant associations with FEV_1, FEV_1/FVC, RV/TLC, and BDR using all CT measurements adjusted by confounding variables. We reported the standardized β coefficients, that are estimates expressed in units of standard deviation so that the independent variables could be compared based on their relative effect on the dependent variable in terms of standard deviation change. A linear mixed effects model using the residual (restricted) maximum likelihood estimation method for the covariance parameters was performed for longitudinal FEV_1 and FEV_1/FVC change; baseline variables included age, sex, BMI, race, smoking status, FEV_1, TAC, and LAA_{950}; interaction terms for baseline TAC, LAA_{950}, and FEV_1 with time were included; time alone was also included in the model.

Results

Participant Demographics, Pulmonary Function, and Imaging Measurements

The participant demographics, pulmonary function, and imaging measurements for all 1,184 participants evaluated ($n = 286$ never-smokers without airflow limitation, $n = 298$ at-risk, $n = 361$ GOLD I, $n = 239$ GOLD II COPD) are provided in Table 1. GOLD I participants were significantly older than participants in the at-risk group ($P = 0.03$) and had fewer females than the never-smoker ($P = 0.0007$) and at-risk ($P = 0.01$) groups. There were no other differences between the groups for age, sex, race, or BMI. Pack-years smoking and other pulmonary function measurements worsened with increasing disease severity as shown in Table 1.

The imaging measurements showed LAA_{856} and LAA_{950} were significantly elevated and TAC and airway inner area were significantly reduced in GOLD I and II compared with the never-smoker and at-risk groups ($P < 0.05$); TAC and airway inner area were significantly reduced in GOLD II compared with GOLD I COPD ($P < 0.05$). For the subset of participants with PRM measurements, PRM-fSAD was significantly elevated in GOLD II compared with never-smokers and at-risk participants ($P < 0.05$). PRM-emphysema was significantly elevated in GOLD II compared with the never-smokers, at-risk, and GOLD I participants ($P > 0.05$). There were no differences between the never-smokers and at-risk participants for any of the imaging measurements ($P > 0.05$).

What Sizes of Airways Are Reduced with Increasing COPD Disease Severity?

In Figure 2A, three-dimensional CT airway tree reconstructions visually demonstrate the reduction in the total number of airways with increasing disease severity as shown quantitatively in Figures 2B and 2C. The TAC was significantly reduced for airway generations more distal to the segmental airways (generation 3) for GOLD I and GOLD II compared with never-smokers and at-risk ($P < 0.0001$); and GOLD II compared with GOLD I COPD ($P < 0.0001$). Figure 2C shows that the TAC was not significantly different between the groups for airways less than 2.00 mm and 2.00–2.49 mm ($P > 0.05$), but was significantly reduced for all other airway diameter sizes for GOLD I and GOLD II COPD compared with never-smokers and at-risk ($P < 0.0001$) and for GOLD II compared with GOLD I COPD ($P < 0.0001$). The distribution of CT airways by generation and by airway diameter is also shown in Tables E2 and E3 in the online supplement.

Was TAC Reduction with Increasing COPD Disease Severity Independent of Emphysema and Related to Airway Narrowing/Tapering?

Figure 3 shows that TAC was significantly reduced in GOLD I and GOLD II compared with never-smokers ($P < 0.0001$) and at-risk ($P < 0.0001$), after adjusting for confounding variables; TAC was not significantly different between GOLD I and GOLD II ($P > 0.05$). Importantly, these differences persisted after adjusting for LAA_{950} whereby TAC was significantly reduced by 19% in both GOLD I and GOLD II compared with never-smokers ($P < 0.0001$), and by 17% in both GOLD I and GOLD II compared with at-risk ($P < 0.0001$) participants.

The three-dimensional reconstructions of the segmented airway tree along with the two-dimensional airway path from the trachea to the sub-subsegmental daughter branch for RB1 for two representative participants show that the parent airway diameter was significantly decreased in the participant with a missing daughter branch (Figure 4B) compared with the participant without a missing daughter branch (Figure 4A). In all participants, Figure 4C shows that those with missing daughter branches had parent airways with significantly narrowed lumen diameters ($P < 0.0001$), reduced airway wall area ($P < 0.0001$), and greater lumen diameter tapering ($P < 0.0001$) than those participants with no missing daughter branches. Moreover, for parent airways, the decrease airway lumen diameter ($P < 0.0001$), decrease in airway wall area ($P < 0.0001$), and increase in airway lumen tapering ($P = 0.002$) all remain

Table 1. Subject Demographics, Pulmonary Function, and Imaging Measurements

Parameter	Never-Smoker (*n* = 286)	At-Risk (*n* = 298)	GOLD I (*n* = 361)	GOLD II (*n* = 239)
Subject demographics				
Age, yr	66 (10)	66 (9)	68 (10)*	66 (10)
Female sex, *n* (%)	136 (48)	131 (44)	124 (34)*†	100 (42)
White, *n* (%)	266 (93)	283 (95)	347 (96)	223 (93)
Pack-years, yr	0 (0)	21 (24)†	18 (23)†	26 (26)*†‡
BMI, kg/m^2	27 (5)	28 (5)	27 (4)	28 (6)
Current-smoker, *n* (%)	—	64 (21)	52 (14)*	61 (26)
History of asthma, *n* (%)	21 (7)	30 (10)	66 (18)*†	86 (36)*†‡
History of tuberculosis, *n* (%)	3 (1)	0 (0)	5 (1)	5 (2)*
History of HDHTDM, *n* (%)	97 (34)	106 (36)	131 (36)	115 (48)*†‡
History of bronchiectasis, *n* (%)	54 (19)	48 (16)	75 (21)	48 (20)
Pulmonary function				
FEV_1, $\%_{pred}$	106 (15)	103 (14)†	96 (12)*†	69 (8)*†‡
FEV_1/FVC, %	78 (5)	77 (5)	64 (5)*†	59 (8)*†‡
RV/TLC, %	37 (8)	37 (7)	40 (9)*†	46 (9)*†‡
D_{LCO}, $\%_{pred}$	115 (23)	113 (22)	109 (23)†	94 (24)*†‡
BDR FEV_1, %	4 (30)	3 (31)	7 (45)*†	10 (49)*†‡
Imaging				
LAA_{856}, %	21 (17)	18 (15)	29 (16)*†	31 (19)*†
LAA_{950}, %	3 (3)	3 (3)	5 (5)*†	5 (5)*†
TAC, *n*	221 (73)	217 (68)	190 (66)*†	152 (53)*†‡
Pi10, mm	3.9 (0.1)	3.9 (0.1)	3.9 (0.1)	3.9 (0.1)
Inner area, mm^2	12.1 (4.6)	11.8 (3.2)	10.8 (3.1)*†	9.5 (2.6)*†‡
PRM fSAD, %§	12 (13)	10 (11)	18 (15)*†	21 (17)*†
PRM Emph, %§	0.02 (0.06)	0.02 (0.03)	0.17 (0.62)	0.55 (2.24)*†‡

Definition of abbreviations: $\%_{pred}$ = percent predicted; BDR = bronchodilator response; BMI = body mass index; Emph = emphysema; fSAD = functional small airway disease; GOLD = Global Initiative for Chronic Obstructive Lung Disease; HDHTDM = heart disease, systemic hypertension, or diabetes mellitus; LAA_{856} = low-attenuation area of the lung with attenuation values below −856 Hounsfield units on full-expiration computed tomography; LAA_{950} = low-attenuation area of the lung with attenuation values below −950 Hounsfield units on full-inspiration computed tomography; Pi10 = the square root of the airway wall area for a theoretical airway with 10-mm internal perimeter; PRM = parametric response map; RV = residual volume; TAC = total airway count; TLC = total lung capacity.

Data are shown as mean (SD) unless otherwise specified.

*Significantly different from at-risk ($P < 0.05$).

†Significantly different from never-smoker ($P < 0.05$).

‡Significantly different from GOLD I ($P < 0.05$).

§$n = 140$, $n = 103$, $n = 149$, and $n = 102$ in never-smokers, at-risk, GOLD I, and GOLD II, respectively.

independently significantly associated with daughter branches missing or not missing after adjusting for confounding variables in a multivariable logistic regression model (*see* Table E4).

Further analysis (*see* Table E5) in a subgroup of participants ($n = 494$) in which PRM measurements were obtained showed in a multivariable regression model after adjusting for confounding variables that TAC was significantly and negatively associated with PRM-fSAD measurements ($P = 0.0002$), but not PRM-emphysema ($P = 0.53$).

Was TAC the Dominant Contributor to Pulmonary Function?

Table 2 shows the results of multivariable regression analysis for pulmonary function measurements that included all CT measurements in the same model in all participants adjusted for cofounding variables. Among all imaging measures investigated, the standardized beta coefficients (β) indicated that TAC ($\beta = 0.18$; $P < 0.0001$) had the greatest relative influence on FEV_1, followed by LAA_{950} ($\beta = -0.14$; $P < 0.0001$) and inner area ($\beta = 0.06$; $P = 0.02$). TAC ($\beta = 0.40$; $P < 0.0001$) also had the greatest relative influence on FEV_1/FVC, followed by LAA_{950} ($\beta = -0.20$; $P < 0.0001$), LAA_{856} ($\beta = -0.12$; $P < 0.0001$), and inner area ($\beta = 0.08$; $P = 0.009$). For RV/TLC, Pi10 ($\beta = -0.13$; $P < 0.0001$) and TAC ($\beta = -0.12$; $P = 0.0008$) had the greatest relative influence followed by LAA_{856} ($\beta = 0.10$; $P = 0.003$). For BDR, significant associations were shown for both TAC ($\beta = -0.27$; $P < 0.0001$) and LAA_{856} ($\beta = 0.12$; $P = 0.0004$), although the TAC had the greatest relative influence. The relative influence of TAC was also greater than all other imaging measures on FEV_1, FEV_1/FVC, and BDR when the GOLD I and GOLD II COPD groups were investigated separately (*see* Tables E6–E9).

Was TAC Associated with Longitudinal Lung Function Decline?

Table 3 shows multivariable linear mixed effects regression models for longitudinal FEV_1 and FEV_1/FVC decline in all participants that included CT TAC and LAA_{950} in the same model and was adjusted for baseline cofounding variables (age, sex, BMI, race, smoking status, FEV_1); the expanded table with all parameters is shown in Table E10. Over an approximately 6-year time frame, TAC was significantly associated with longitudinal decline in FEV_1 ($P = 0.02$) and FEV_1/FVC ($P = 0.01$) independent of LAA_{950} and baseline FEV_1.

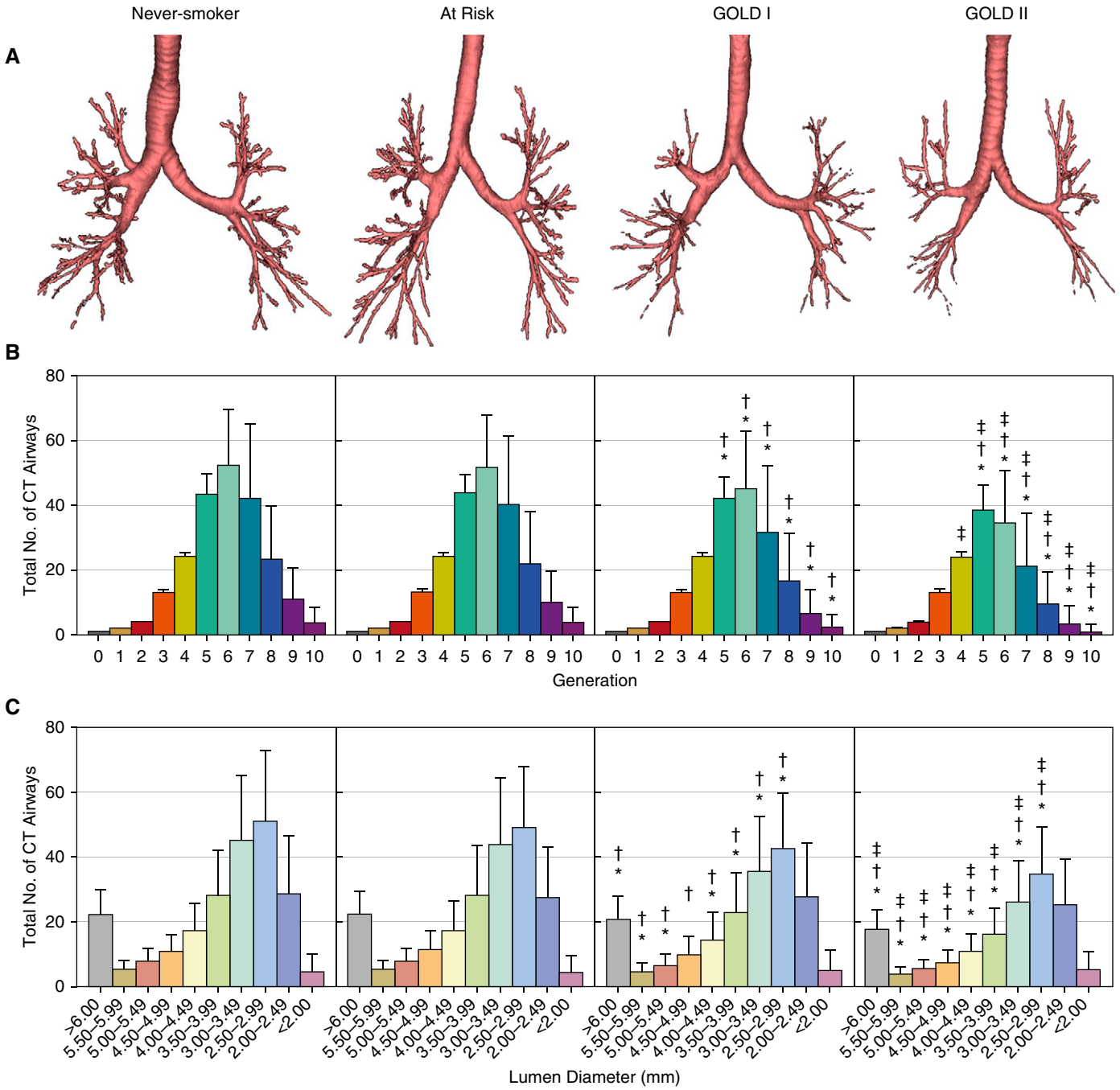

Figure 2. Computed tomography airway count by generation and airway lumen diameter. The three-dimensional reconstruction of the segmented airway tree generated by VIDA Diagnostics Inc. for never-smokers and participants at risk and with Global Initiative for Chronic Obstructive Lung Disease (GOLD) I and GOLD II chronic obstructive pulmonary disease (*A*). The plot summary data show airway counts for airways color coded by airway generation (*B*) and by various sizes divided into discrete bins (*C*). Error bars represent the SD of the airway counts for all participants. *Significantly different from never-smoker. †Significantly different from at-risk. ‡Significantly different from GOLD I. CT = computed tomography.

Discussion

The development of effective therapies for COPD requires a thorough understanding of the disease pathogenesis. With increasing evidence pointing to small airway destruction as the precursor to emphysema development (3), sensitive tools are needed that can identify small airway disease in the earliest stages. Although reduction in the number of terminal bronchioles measured using micro-CT has been shown to occur early in the disease course (3), few studies have investigated the TAC *in vivo* using CT. Diaz and colleagues (17) demonstrated that the total number of CT airways correlates with emphysema extent, pulmonary function measurements, and dyspnea in

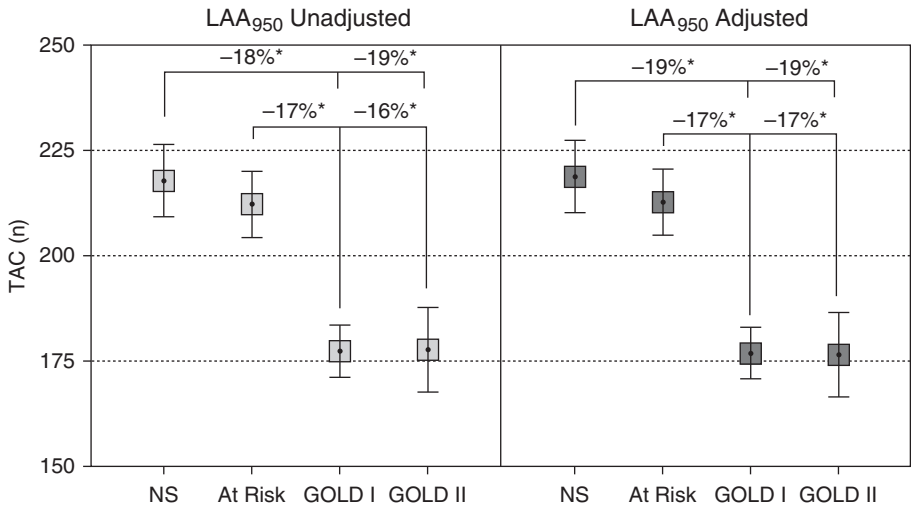

Figure 3. Computed tomography (CT) airway count unadjusted and adjusted by low-attenuation areas of the lung below −950 Hounsfield units (LAA_{950}) for never-smokers and participants at risk and with Global Initiative for Chronic Obstructive Lung Disease (GOLD) I and GOLD II chronic obstructive pulmonary disease. The total airway count was significantly reduced in GOLD I and GOLD II compared with never-smokers ($P < 0.0001$) and at-risk ($P < 0.0001$) in both LAA_{950} adjusted and unadjusted models. Also adjusted by age; sex; race; pack-years; smoking status; body mass index; history of asthma; history of tuberculosis; history of history of heart disease, systemic hypertension, or diabetes mellitus; bronchiectasis, CT air volume; and CT model. The boxes are centered on the mean, and the whiskers represent the 95% confidence intervals. *Significantly different (<0.05). NS = never-smoker; TAC = total airway count.

COPD. However, the cohort of participants investigated by Diaz and colleagues (17) had severe emphysema and therefore it is unknown whether reduced CT airway count occurred before emphysema development.

To our knowledge, there have been no studies investigating CT airway count in a population-based sample of participants at risk and with milder COPD. Our findings extend important early observations (17), and here in this population-based study we report the following: *1*) compared with at-risk participants, TAC was reduced by 17% in mild (GOLD I) COPD, independent of emphysema; *2*) missing airways were spatially related to airway luminal narrowing and tapering, and wall thinning of parent airway segments; *3*) among all CT measurements investigated, TAC had the greatest relative influence on pulmonary function; and *4*) reduced TAC was independently associated with longitudinal lung function decline over a 6-year time frame. Importantly, these findings also extend early observations by demonstrating the feasibility and applicability of this analysis by using CT images acquired with standard CT image acquisition protocols across varying CT platforms and at various sites using commercially available software.

In comparison with other large COPD cohort studies that recruit from outpatient clinics of large medical centers, such as COPDGene (Genetic Epidemiology of COPD) (18), ECLIPSE (Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points) (19), and SPIROMICS (Subpopulations and Intermediate Outcomes in COPD Study) (20), participants recruited from population-based studies like CanCOLD have earlier and milder forms of COPD and, consequently, lower levels of emphysema. In these participants with low levels of emphysema, we demonstrated that the number of CT airways was reduced in GOLD I and GOLD II COPD compared with never-smokers and at-risk participants in the fourth generation and beyond. Furthermore, we demonstrated that various sized airways were reduced in GOLD I and GOLD II COPD, except for airways less than 2.50 mm in diameter. These findings that airway counts are reduced in GOLD I and GOLD II COPD are in accordance with the findings by McDonough and colleagues (3). Although McDonough and colleagues (3) showed that the number of CT airways 2.0–2.5 mm in diameter was reduced in COPD, the airways in this study were manually counted, whereas the current investigation used commercially available airway segmentation software. Because airways of this size are approaching the CT resolutions limits, it is likely that the automated software does not perform as well as an experienced observed and therefore the software may not have counted enough airways 2.0–2.5 mm in diameter to reach statistical significance between the groups. However, it must be noted that manual airway segmentation and airway counting requires a significant amount of time therefore limiting its applicability in routine COPD management. Furthermore, we note that other validated, automated CT software for airway analysis also reports airway segmentation up to the 14th generation, supporting the notion that the CT smaller airways can be reproducibly evaluated (21, 22).

Importantly, our finding that TAC, which includes all measured airways, was reduced even in mild (GOLD I) COPD participants using commercially available software indicate that this analysis could be feasible and widely applicable using routine CT image acquisition protocols across various sites and CT platforms. Interestingly, the finding that airway counts were reduced in airways of various sizes, and not only the smaller airways, suggests narrowing, obstruction, and/or destruction occurs more uniformly throughout the airway tree. Moreover, the finding that TAC was reduced in GOLD I and GOLD II COPD independent of emphysema suggests that emphysematous destruction is not the only factor driving the reduction in airway count.

We next investigated other factors that may be driving the reduction in CT airway count and found that participants with parent airway segments with missing daughter branches had significantly reduced lumen diameters, thinner airway walls, and significantly more tapered airways than participants with airways not missing a daughter branch. These findings suggest that airway luminal narrowing and wall thinning make it difficult to resolve distal, daughter airways using CT. This is supported by Smith and colleagues (9) findings that CT airway walls are thinner in COPD compared with control subjects. Although we cannot determine in the

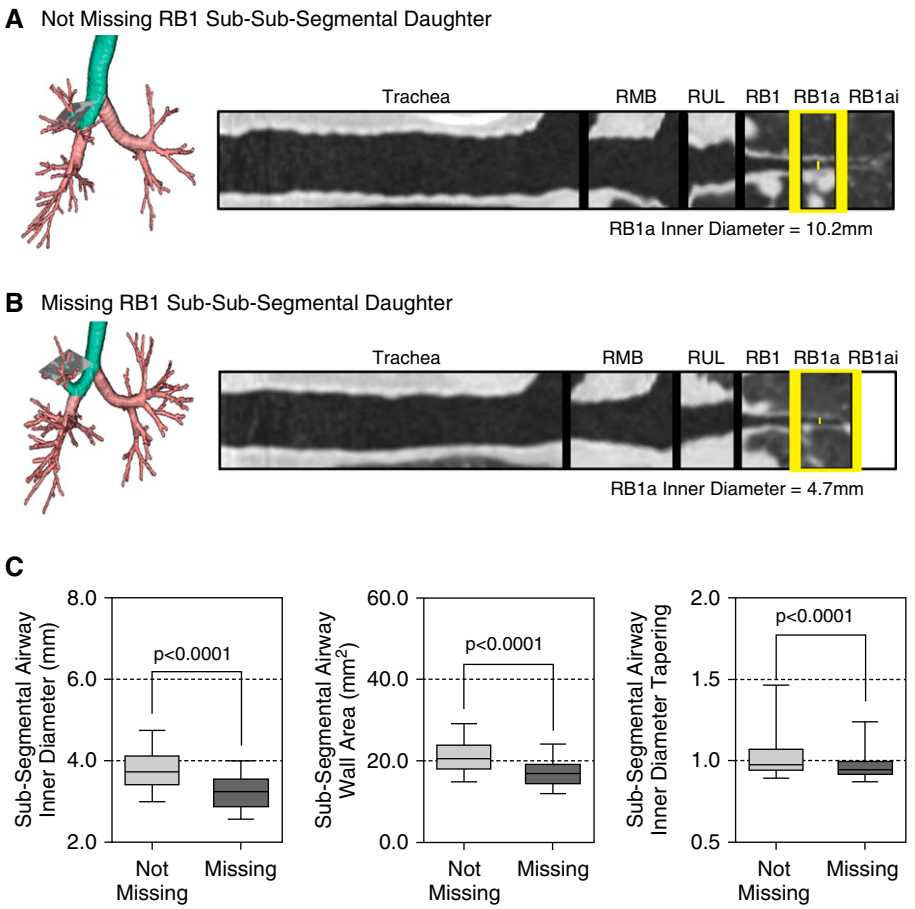

Figure 4. Subsegmental airway lumen diameter and airway tapering and airway wall area percent measurements for participants with subsegmental airways either not missing or missing their sub-subsegmental daughter branches. The three-dimensional reconstruction of the segmented airway tree with the path to RB1 highlighted in green along with the two-dimensional airway path from the trachea to the sub-subsegmental daughter branch of RB1 (RB1ai) for a participant with their sub-subsegmental daughter branch not missing (*A*) or missing (*B*). The subsegmental RB1 daughter branch (RB1a) distal to the missing airway is highlighted in yellow, and the airway inner diameter measurements are shown below. For all subsegmental airways evaluated, the inner diameter, airway wall area, and inner diameter tapering measurements were significantly reduced for all participants with a daughter branch missing ($P < 0.0001$) compared with those with a daughter branch not missing (*C*). The box extends from the 25th to 75th percentiles, the middle line is the median, and the whiskers represent the 5–95 percentiles. Significance of difference (*P*) was determined using Mann-Whitney *t* test ($P < 0.05$). RB1 = apical segment of the right upper lobe bronchus; RMB = right main bronchus; RUL = right upper lobe.

current study exactly what caused airways to appear as missing in CT, whether it be airway luminal narrowing caused by excessive bronchoconstriction, mucus occlusion, or airway wall thinning due to degradation of the walls, our findings suggest it is at least in part related to structural abnormalities in the airways. Although only a small subset of the participants were investigated, this notion was also supported by the finding that TAC was significantly associated with PRM fSAD measurements, independent of emphysema.

TAC was also shown to have the greatest relative influence on pulmonary function measurements (FEV_1, FEV_1/FVC, RV/TLC, and BDR) among all the CT measurements investigated. CT airway count therefore provided unique information related to pulmonary function independent of the extent of emphysema, the extent of expiratory gas trapping, remodeling of the airway walls, and segmental airway luminal narrowing. Furthermore, the finding that TAC was significantly associated with pulmonary function independent of segmental airway luminal narrowing suggests that TAC reflects luminal narrowing not only in central airways, but also more distal airways. We note that CT gas volume and bronchiectasis were included as confounding variables and therefore this finding was not a direct result of more CT airways visible due to great lung volumes or more dilated airways. We also note that our finding that TAC was significantly associated with airflow limitation in never-smokers (*see* online supplement) was surprising and suggests that lung development may play a role in reduced airway count. Diaz and colleagues (23) also provided evidence that CT airway dimension measurements are related to airflow limitation in never-smokers, which supports this notion. Whether individuals with reduced TAC may be more susceptible to the development of COPD (i.e., they may have different lung function trajectories [24]) is an important question, and although it is beyond the scope of this study to investigate, it is one that deserves further investigation.

Finally, we showed that participants with reduced TAC had accelerated lung function decline over the 6-year time frame, irrespective of baseline FEV_1, emphysema, and other confounding variables. Initiating treatment in patients with or at risk of COPD with early airway-related disease changes before emphysema develops may hold the greatest promise for slowing disease progression. Our findings indicate that CT airway count may serve as an imaging biomarker reflecting airway-related structural changes. Therefore CT TAC may be useful to stratify patients with reduced TAC into clinical trials to enrich clinical trials with participants with early evidence of airway abnormalities or to serve as a sensitive intermediate endpoint to evaluate the impact of novel COPD treatment. However, evaluating CT TAC longitudinally to determine if reduced TAC over time is associated with clinical outcomes, and pathologic validation, is required before the potential of this measurement in clinical trials can be realized. Furthermore, an unmet need in COPD patient management is identifying patients at the greatest risk of accelerated disease progression. Our findings indicate that patients with reduced CT TAC have accelerated lung function decline. Although there are currently limited treatment options for

Table 2. Multivariable Regression Models for Pulmonary Function Measurements with All Imaging Measurements Included in the Same Model in All Participants

	Standardized Estimate	SE	Variance Inflation Factor	*P* Value
FEV_1*, L				
LAA_{856}	−0.04	0.0009	1.61	0.08
LAA_{950}	−0.14	0.004	1.67	<0.0001
TAC	0.18	0.0002	1.89	<0.0001
Pi10	0.007	0.11	1.36	0.72
Inner area	0.06	0.005	2.01	0.02
FEV_1/FVC*				
LAA_{856}	−0.12	0.01	1.61	<0.0001
LAA_{950}	−0.20	0.06	1.67	<0.0001
TAC	0.40	0.004	1.89	<0.0001
Pi10	−0.02	1.69	1.36	0.48
Inner area	0.08	0.08	2.01	0.009
RV/TLC*				
LAA_{856}	0.10	0.0002	1.60	0.003
LAA_{950}	0.04	0.0007	1.69	0.24
TAC	−0.12	0.00004	1.87	0.0008
Pi10	−0.13	0.02	1.37	<0.0001
Inner area	−0.05	0.0009	1.99	0.16
BDR FEV_1*, %				
LAA_{856}	0.12	0.0002	1.61	0.0004
LAA_{950}	0.04	0.0006	1.67	0.22
TAC	−0.27	0.00004	1.89	<0.0001
Pi10	−0.002	0.02	1.36	0.95
Inner area	−0.06	0.008	2.01	0.13

Definition of abbreviations: BDR = bronchodilator response; CT = computed tomography; LAA_{856} = low-attenuation area of the lung with attenuation values below −856 Hounsfield units on full-expiration CT; LAA_{950} = low-attenuation area of the lung with attenuation values below −950 Hounsfield units on full-inspiration CT; Pi10 = the square root of the airway wall area for a theoretical airway with 10-mm internal perimeter; RV = residual volume; TAC = total airway count; TLC = total lung capacity.
*Adjusted by age; sex; race; pack-years; smoking status; body mass index; history of asthma; history of tuberculosis; history of heart disease, systemic hypertension, or diabetes mellitus; bronchiectasis; CT air volume; and CT model.

patients with COPD, a measurement that can indicate which patients are at increased risk of accelerated disease progression would enable clinicians to more carefully monitor those patients over time.

This study has limitations that deserve mention. We must note that histologic validation of TAC in explanted lung tissue was beyond the scope of this study, but is critical in understanding the factors dominating TAC reduction in patients with varying stages of COPD. Although pathology validation is complex, using a novel approach that links CT to micro-CT and histology in exactly the same *ex vivo* samples of tissue (25) will enable the investigation of whether small airways disease in the lung's quiet zone (preterminal and terminal bronchioles) is reflected in the more central airways as measured by TAC. We also acknowledge that the longitudinal data collection for this study is still ongoing, and therefore the number of participants with complete longitudinal data ($n = 638$) was limited as was the longitudinal time frame of approximately 6 years. Another important limitation is the fact that CT was acquired at nine centers that used a variety of CT models by different manufacturers, and we did not use a phantom to standardize CT measurements at each center. Although we adjusted for CT model in our multivariable linear regression models, we acknowledge this is a limitation. We note that our image acquisition protocol was based on the image acquisition protocol used in the COPDGene cohort study (18). Furthermore, we acknowledge efforts of the Quantitative Imaging Biomarkers Alliance Lung Density Committee to conduct phantom studies to assess the measurement variation attributed to different CT manufacturers (26). Reducing this nonbiologic CT measurement variability will allow for more reproducible measurements, which is clearly important for future multicenter studies.

In conclusion, although pathologic validation is needed these findings suggest CT TAC may reflect the same airway-related disease changes observed in the small airways, the "quiet" zone of the lung (27), that significant reduction in TAC occurs in very mild COPD, and that reduced TAC predicts more rapid lung-function decline. Taken together, these findings indicate that early intervention may be required for optimal disease modification. ■

Table 3. Mixed Effects Multivariable Regression Models for Longitudinal Lung-Function Decline

Interactions	Estimate (95% CI)	SE	*P* Value
Model 1: FEV_1*, ml			
FEV_1 × time	−17.53 (−20.74 to −14.32)	1.64	<0.0001
TAC × time	0.04 (0.01 to 0.08)	0.02	0.02
LAA_{950} × time	−0.86 (−1.42 to −0.29)	0.29	0.003
Model 2: FEV_1/FVC*, %			
FEV_1 × time	−0.008 (−0.08 to 0.06)	0.03	0.81
TAC × time	0.0009 (0.0002 to −0.002)	0.0004	0.01
LAA_{950} × time	−0.02 (−0.03 to −0.007)	0.006	0.002

Definition of abbreviations: CI = confidence interval; LAA_{950} = low-attenuation area of the lung with attenuation values below −950 Hounsfield units on full-inspiration computed tomography; TAC = total airway count.
*Also included in the model: time and baseline age (yr), sex (female), body mass index (kg/m^2), white, smoking status, FEV_1 (L), TAC (n), and LAA_{950} (%).

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